The historical feud over polio vaccine: how could a killed vaccine contain a natural disease?

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Summary points

- The Salk killed-virus polio vaccine, developed in 1953 and field-tested the following year under the sponsorship of the National Foundation for Infantile Paralysis, faced great opposition from virologists, including the Foundation's own advisors.
- The controversy over the Salk vaccine appeared to be a debate over the risks and benefits of killed-virus versus live-virus vaccines, with attendant criticism of the publicity surrounding the vaccine's introduction.
- The deeper conflict between advocates and opponents of the Salk vaccine was between two models of biomedical research.
- Salk and his supporters understood viral infection and immunologic response as mechanistic processes, which could be replicated and manipulated by laboratory methods.
- Salk's opponents described viral research as the controlled observation of life processes, to further understand those processes for clinical application.

"How dare I claim that the world is round, not flat?" a beleaguered Jonas Salk protested to his biographer, Richard Carter, in the early 1960s.[1] Salk usually argued in more technical terms, yet his frustration over scientific attacks on his inactivated ("killed") virus polio vaccine was evident. The February 1997 decision of the US Advisory Committee on Immunization Practices to recommend increased reliance on inactivated polio virus—designed to reduce the incidence of vaccine-associated polio linked to Albert Sabin's oral live-virus vaccine—marked the end of four decades of controversy and represented a partial vindication of Salk and his sponsors, the National Foundation for Infantile Paralysis.[2] In June this year a federal advisory panel went further, recommending that the United States abandon the oral vaccine, a recommendation expected to be accepted by the Centers for Disease Control and Prevention.

In recent years Salk and Sabin, and their supporters, have couched the debate in the language of cellular and genetic immunology. Historical accounts of their rivalry have often cited the intense publicity that surrounded the introduction of Salk's vaccine as the reason for its long disfavor among scientists.[3] In 1953, however, lacking present-day understanding of antibody formation, virologists debated the vaccine question instead in terms of the nature and meaning of biomedical research.

Jonas Salk first presented his work to the National Foundation's Advisory Committee on Immunization on 23 January 1953 in Hershey, Pennsylvania. He was then 39 years old, the committee's youngest member. Since completing his residency, he had been supported by National Foundation grants, first working with Thomas Francis at the University of Michigan, then in his own lab in Pittsburgh, where he had spent several tedious years on the "scut work" of typing strains of poliovirus.[4] He had developed an exacting multistep process of inactivating the three known strains with formalin and combining them in a "killed-virus" vaccine. During 1951 and 1952, he had tested this preparation on 161 children who lived in institutions. The children had shown no ill effects, and their antibody titers had risen significantly.[4]

Several committee members were impressed with Salk's presentation and recommended scheduling a field trial of his vaccine. But virologist John Enders, a Nobel laureate, advised a more deliberate strategy: "I would suggest more experimentation along the lines that he is doing so admirably at the moment, and not enter into a large experiment which will inevitably be connected with a lot of publicity and may jeopardize the entire program." Albert Sabin of the University of Cincinnati, who was attempting to develop a live-virus vaccine, supported Enders.[4,5]

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Jonas Salk vaccinating a child

Sabin referred to the events that followed as "the mess after Hershey."[6] Within a week, the foundation held a press conference, promising field-testing of a polio vaccine within a year, then followed the press conference with a flurry of publicity releases.[7,8] On 25 May, Thomas Rivers of Rockefeller Hospital, dean of the foundation's scientific advisors, created a new Vaccine Advisory Committee to supervise the planned trials. Only two virologists from the Committee on Immunization were asked to serve; the rest of the members of this new group were specialists in public health or internal medicine.[4]

Clearly, Rivers and the foundation had determined, soon after hearing of Salk's initial results, to move ahead with a field trial, to draw support from public opinion and the general medical community, and to remove or neutralize the opposition of some virus experts. In the latter objective they hardly succeeded, in that criticisms of the Salk vaccine persisted even after the success of the 1954 trials. Some critics attacked the high-handed usurpation of scientific prerogative by a lay volunteer group and the amount of publicity about the vaccine. But Enders, Sabin, and their colleagues directed their fire at the scientific deficiencies of the Salk vaccine. They asserted the superiority of an attenuated vaccine, as in the cowpox/smallpox model, one without sufficient virulence to produce paralytic disease but potent enough to stimulate permanent immunity.

The relationship between antibody and resistance

Salk did not dispute the rationale behind a live-virus vaccine, but he did challenge its preeminence as a model. Ten years of work had led him to "the now reasonable assumption that the relationship between antibody and resistance is more than one of mere association—that it is one of cause and effect," and to the related belief that antibodies seen in the blood of persons who had recovered from a disease were not merely by-products of infection but indeed the agents of subsequent immunity.[9] He had demonstrated experimentally that "poliomyelitis virus is a relatively potent antigen," one that generated high antibody levels and, he contended, effective immunity.[10]

The problem was to stimulate antibody production without running the risk of paralysis or death; as the solution, Salk proposed a highly antigenic strain of poliovirus, inactivated under very specific conditions of time, heat, formalin concentration, and acidity. He argued that his precise and painstakingly developed specifications guaranteed that the virus would not be lethal.[11]

Salk's experiments with monkeys, and later with children, had shown that his process generated a safe vaccine, and one that would produce the antibody levels that he equated with immunity. The question remained whether the postulated immunity would endure throughout life. While the debate raged during 1953, he continued his tests, demonstrating that a child once vaccinated reacted to a second injection with even higher antibody titers; this booster effect, Salk thought, ensured that any subsequent infection with the natural virus would be met with a horde of antibody; therefore, immunity from a killed virus would be lasting.[9-11]

He had been cautious in presenting his early results, hesitant to consider a large field trial; but in March 1953, he was already confident of his method and his vaccine.[4] He became increasingly dismayed as he found that "the idea of a live-virus vaccine has exerted, and still does exert, a very powerful influence, and one that seems to determine not only attitudes and opinions, but policy for action as well"—although, since no attenuated virus that could be safely and effectively used for vaccination had been found, "there has been not much to discuss except the idea."[10]

Salk recalled to Richard Carter some years later: "What had once been skepticism about attempts to develop an effective killed vaccine was now becoming ideological conflict. How could a killed vaccine contain the magical life force of the natural disease?"[1]

An ideological conflict

Salk's former mentor, Thomas Francis, who directed the field trials, had described the ideological conflict more dispassionately in 1955: "The two outlooks, then, are simply this: inactive virus vaccine is apparently a test of the straightforward hypothesis that antibody induced by the administration of antigen can provide protection without subjecting the recipient to harmful effects of even the inapparent infection. The other, through the use of modified active virus, seeks to induce antibody formation, but wishes to add some undesignated advantage derived from apparently harmless infection."[12]

What were the advantages attributed to live-virus vaccine?

Albert Sabin, a Polish emigré only eight years older than Salk, had worked with polio cultures since the 1930s. In 1953, with National Foundation support, he was attempting to isolate an attenuated virus by identifying the least active viruses in a tissue culture, reculturing these, then repeating the process with each successive generation. There may have been a degree of self-interest in his critique of the Salk vaccine, but he was strongly seconded by Enders, Herald Cox (who had worked with live virus at Lederle Laboratories), and others of weight and reputation.

In June 1953, Sabin opened a presentation at an American Medical Association meeting by saying, "Since there is an impression that a practicable vaccine for poliomyelitis is either at hand or immediately around the corner, it may be best to start this discussion with the statement that such a vaccine is not now at hand and that one can only guess as to what is around the corner."[13]

He denied Salk's assumption that antibody production was equivalent to immunity, contending that certain

Albert Sabin

immunity could exist only in an individual who had survived actual infection; and he expressed concern about the safety of the highly antigenic strains used in killed-virus.

Finally, Sabin argued that the Salk vaccine might "interfere with the subclinical infections which under natural conditions immunize the vast majority of the population against poliomyelitis." His conclusion was that, although a safe killed-virus vaccine, if one were possible, might be used as a temporary preventive, "the ultimate goal for the prevention of poliomyelitis is immunization with 'living' avirulent virus, which will confer immunity for many years or for life."[13]

Herald Cox had voiced similar thoughts in April: "I am of the opinion that the most logical and practical way to immunize infants and children against poliomyelitis is to follow the pattern that seems to take place so universally under natural conditions..."[14]

Likewise John Enders had written: "The ideal immunizing agent against any virus infection should consist of a living agent exhibiting a degree of virulence so low that it may be inoculated without risk. Since a decline in the virulence of other viruses has in the past frequently occurred after prolonged cultivation in vitro, one might expect this change also to take place in the agents of poliomyelitis."[15]

The issues of immediate immunity and safety would be resolved by the actual experience of the field trials. But the concept that only a natural infection with a living agent, resembling the actual disease, could confer real immunity could not be addressed with the knowledge and methods available in 1953.

The underlying conflict here is between two concepts of biomedical research. In the Sabin-Enders model, the scientist observes the living organism and describes its natural history and behavior, which may be verified experimentally and then applied to human advantage. In the Salk process, the researcher uses scientific methods, not to observe but to manipulate, changing the organism in a non-natural way and altering the normal course of events. Both models have long antecedents in the history of biology, the former analogous to studies of anatomy and evolution, the latter to "mechanistic conceptions" such as that of Jacques Loeb.[16]

Salk and Francis accused their opponents of a belief in some special quality of the living virus that could not be reduced to physical actions and interactions, a vitalism considered passé in the 1950s.[17]

But the foundation's own research program prior to 1953 had emphasized scientific knowledge of the disease entity over vaccine production. The logical next step for most virologists was the painstaking cultivation and observation of live virus, while small trials using the killed virus gave information about antibody protection and persistence. Ultimately, such patience and rigor should result in the best therapeutic solution. The rapid shift to large-scale vaccine production and testing seemed to many an abandonment of science for technology.

In an era when scientists have developed such an impressive tool kit for manipulation of the most basic molecules of life, and when lucrative patents and public acclaim await their application, it may be worthwhile to review this debate again.

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